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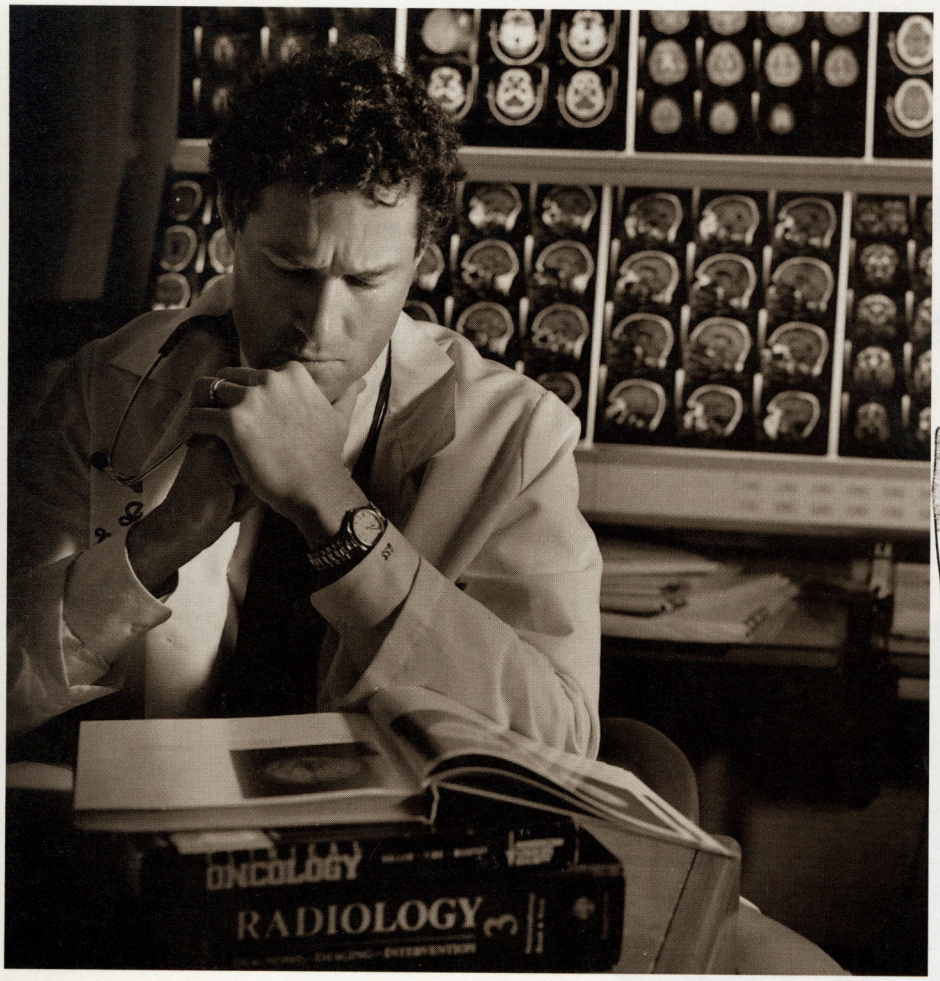
HEALTH & MEDICINE FOR PHYSICIANS

HIPPOCRATES



Ten Great Medical Advances of 1998

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Will doctors who don't disclose their past performance wind up in court? (page 23)

Infectious Disease

Why Nobelist Joshua Lederberg claims the risk of a deadly microbial outbreak is greater than ever (page 50)

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Is there a right way to tell a patient she's dying? (page 44)

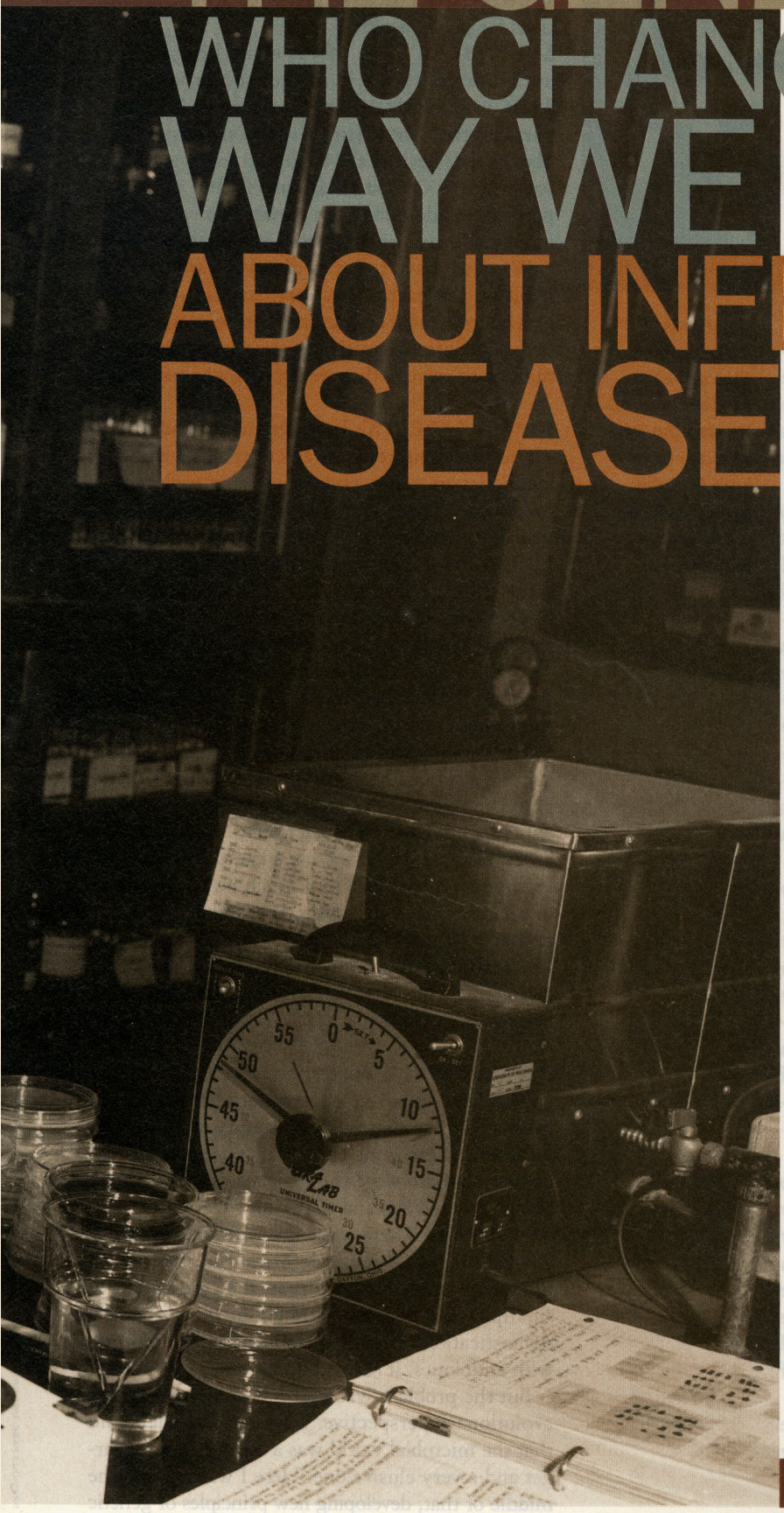
My Most Difficult Diagnosis

Five physicians challenge your clinical know-how with their toughest cases (page 30)

PLUS

Joshua Lederberg in his laboratory at the University of Wisconsin in October 1958.

THE GENETICIST WHO CHANGED THE WAY WE THINK ABOUT INFECTIOUS DISEASE



Meet Nobelist **JOSHUA LEDERBERG,** the dogged researcher who discovered how bacteria evolve and forever altered the way physicians view infection.

MICROBES EVOLVE THROUGH SEX. That simple fact—established by Joshua Lederberg and a fellow scientist in 1946—explains why even antibiotics of last resort are no longer able to kill certain bacteria. That germs exchange genetic information may seem elementary today, but when Dr. Lederberg began his experiments it was unthinkable. Students were taught that a bacterium reproduced by fission, creating two identical cells that then divided, producing identical cells ad infinitum.

This conventional wisdom was upended soon after the young Lederberg accepted an invitation to work with geneticist Edward L. Tatum at Yale. He had just finished his second year at Columbia University's College of Physicians and Surgeons and intended to be gone just three months. As it turned out, he never returned. Instead, he and Dr. Tatum went on to prove that some strains of

E. coli reproduce sexually and share genetic material when they do.

He received a Ph.D. in microbiology when he was 23. At the University of Wisconsin at Madison, where some faculty had challenged his appointment because he was Jewish, Dr. Lederberg and a student showed that a virus could transfer genetic fragments from one bacterium to another. In 1958, for his discoveries about genetic organization and recombination in bacteria, he earned the Nobel Prize in medicine and physiology at age 33—then the youngest person in the biological sciences ever to receive the award. "I thought someone was pulling my leg when I got a call from the press," he recalls. "I didn't want to have an unfounded rumor spread around, have my friends congratulate me, and then have to say, 'Oops—it was all a mistake!'"

A portrait of Dr. Lederberg as a premed student in 1945. He was the first of three boys born to Rabbi Zwi H. and Esther Goldenbaum Lederberg.

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Though Dr. Lederberg won further honors—two years later he was one of a group of 15 scientists named Men of the Year by *Time* magazine—he did not seek out media attention. Instead, he consulted with government agencies on space missions, antibiotic resistance, and biological weapons treaties in an effort to put his scientific knowledge to humane use. The deep sense of responsibility he felt after getting the Nobel Prize also inspired him to try to make science more accessible by writing weekly syndicated newspaper columns on the subject. He chose science as his life's work, he later wrote, because it was as "a path to knowledge of the cosmic order [and] a means of alleviating human suffering."

To this end, he continued to devote himself to research. At Stanford University in the 1960s Dr. Lederberg helped create one of the first computer programs to produce models of organic molecules. In 1978 he was appointed president of the Rockefeller University in New York City, guarding its commitment to basic research while expanding its work on illness and infectious disease; he retired in 1990 and now chairs the school's laboratory of molecular genetics. In 1989 he received the country's highest scientific honor, the National Medal of Science.

Among Dr. Lederberg's greatest contributions to science has been his work on the danger posed by emerging pathogens, which he describes as "our ever-evolving adversary." Arguing for greater health care funding, he has said, "Public health may be thought of as service to the poor, but the stakes are shared by everyone. Further progress will depend very much on doctors embracing the historic root of their name: *docents*—that is, teachers."

Laurie Garrett, a Pulitzer Prize–winning science writer for *Newsday* and author of *The Coming Plague*, interviewed Dr. Lederberg about his work. What follows is adapted from that discussion.

HIPPOCRATES How long ago did we have clear evidence that resistance to antibiotics could be shared between bacteria, and what are the implications for public health?

LEDERBERG Since 1948, when I began using antibiotic resistance in my genetic experiments. Then, in the early 1950s, plasmids, or hereditary particles that live outside the chromosomes, were discovered; besides the chromosomal DNA in the bacterium, it's not at all unusual to find small DNA particles in addition to the chromosome. These are more readily transmitted from one cell to another.

What we have today is the evolution of a bad habit on the part of bacteria. Bacteria that have grown up to resist antibiotics in one ecological context can confer that resistance by passing their plasmids on to bacteria that are important to our health.

HIPPOCRATES We have physicians today who argue that drug resistance is overstated and that antibiotics are still as powerful a set of tools as they ever were. There seems to be a phenomenon of denial, to some degree, in the medical community.

LEDERBERG The doctors I see wouldn't put it in quite those terms. They'd rather just keep their fingers crossed and hope for the best. They hope their own patients are not going to suffer from the consequences of drug resistance. That hope is disappointed more and more, and there have been some ghastly events occurring lately.

The development of vancomycin-resistant enterococci is a serious problem of hospital-based infections throughout New York City. We don't have any antibiotics to back up vancomycin; it's an antibiotic of last resort. If staphylococci acquire a vancomycin resistance, it will lead to a much more prevalent, much graver set of infections. Unless the drug industry gets busy and hurries up to fill the pipeline, we just won't have antibiotics appropriate for those indications. It will bring us right back to the 1930s, before we had antibiotics.

HIPPOCRATES How terribly ironic. In the early 1960s there was a sense of extraordinary optimism in this country that we had conquered infectious diseases. At the same time, the very tools we had come to believe were the basis for optimism were being rendered less and less useful.

LEDERBERG There was a great exuberance about what were indeed great victories: the abolition of polio as a major health threat, the eradication of smallpox as a disease throughout the globe, the domestication of many serious infectious diseases with antibiotics. It really did look very, very good.

But the problem was that few clinicians had an evolutionary perspective. They didn't understand that the microbial world was a rapidly moving target and a very elusive one. Here I was right in the middle of that, developing new principles of genetic

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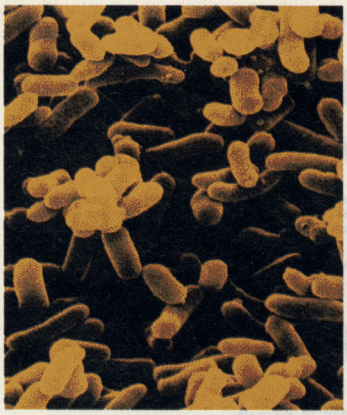
plasticity for bacteria—that is, their ability to change. So I knew differently. I could see that world was going to involve a continuing struggle among newly evolving organisms looking for ecological niches and that we couldn't relax our vigilance.

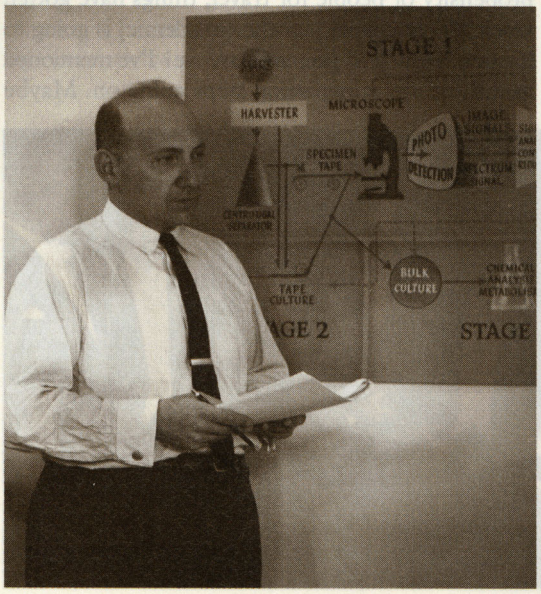
HIPPOCRATES It seems that even as the first warning shots across the bow were being fired by you and a number of other leading scientists and researchers, they were largely being ignored both at the policy level and at the hospital level.

LEDERBERG The shot across the bow couldn't really be ignored. In fact, it wasn't across the bow; it was right into the guts of the ship. It was HIV. When the initial outbreak of HIV was reported, few people were able to foresee what a pandemic the AIDS epidemic was going to be. That's what it has proven to be, and that has really woken people up. I still had to fight the idea that nothing else like AIDS has ever happened. In some respects it is unique. But in others, well, I wrote an article in the mid-1980s called "Pandemic as a Natural Evolutionary Phenomenon," trying to establish that there's a never-ending struggle between man and microbes.

And at a three-day meeting of virologists [at the Rockefeller University in 1988] there were guys who studied viruses in dolphins or in dogs, who studied things like influenza and retroviruses like the ones that cause AIDS. All had seen looming problems [in their own specialties] but they'd never realized that the kinds of new diseases they were seeing in their niches were what everybody else was seeing as well. The mood went from "Gee, I don't know why we're all here, but it's kind of fun to meet everybody" to "Whoa, we're all getting kind of nervous. We're getting collectively worried. And even"—I remember—"a little scared." Next there was an Institute of Medicine study that covered much the same data. And again there was a unanimity that we had been sleeping at the switch when it came to the recognition of the emergence of disease.



E. coli (above). Working with Edward Tatum, Dr. Lederberg proved the bacteria attach and exchange chromosomes (i.e., they have a sex life of sorts).



In the 1950s Dr. Lederberg began a campaign to create new guidelines for space missions, ensuring that no contaminated material would be brought to or from the moon, Mars, or other destinations.

HIPPOCRATES The threat being what?

LEDERBERG The threat may be of outbreaks; it may be of limited or less limited duration. People remind us that the developing world has always been living in a sea of infection. Half the mortality of the world's population has come from communicable disease. The fifth of the world that lives in relative affluence is the exception in that regard. Part of the general myopia is that people are only looking for developments in their own country and not looking at other continents to see the serious epidemics that continue to rage.

HIPPOCRATES There will still be physicians who say, "What are you talking about? You're exaggerating, you're sensationalizing. I still have most of my patients ending up in the cardiology ward."

LEDERBERG In this country, yes, that's undoubtedly correct. Infectious disease right now accounts for 10 percent of the mortality, maybe 15 percent of the morbidity. The point of concern within the United States and economically advanced countries is the possibility of new plagues. These could be substantial outbreaks. The one I tend to use as my model is the 1918 influenza pandemic. It certainly took at least 20 million, some say 25 million, lives—half a million Americans, at a time when the population was only 40 percent of what it is today.

That was a very real event, and there's no reason in the world to believe that it's not going to recur. The evolutionary phenomenon, the rescrambling of influenza genes that generates strains like that, is in fact happening all the time. Our present modes of vaccine development are just not going to be nimble enough to keep up with the spread of a new influenza in a day of instantaneous travel.

It's almost an exaggeration to say that it takes 36 hours to get from any point of the globe to any other point. For all reasonable purposes, it's 12 to 14 hours. That's a very, very short period of time. It's much shorter than the incubation period of most diseases, and we can be quite certain that the next flu pandemic is going to spread far more rapidly than previous ones did simply because of this totally indiscriminate travel.

We could improve our vaccine development capability. There is an effort going on right now at the National Institutes of Health that's beginning to take the first steps to do that. It's far from consummated. If we relied on our current procedures, we could—with very great luck—produce a new vaccine in six months. The standard interval is about nine

"BUGS ARE LIVING IN A WORLD IN WHICH WE'VE BEEN DEVELOPING IMMUNITY TO THEM. AND SOME HAVE BEEN SMART ENOUGH TO DEVELOP COUNTERMEASURES."

months between the time a strain of virus is recognized and the time a vaccine is really available for distribution on a large scale.

HIPPOCRATES In addition to turnaround time, isn't there an issue with the quantity of vaccine we could produce?

LEDERBERG Even in the best-case scenarios, with respect to providing a vaccine to the United States, it wouldn't begin to cover world needs. But there's not even that much optimism about keeping up with the potential need in the United States using current methods.

HIPPOCRATES I think most people assume that we can make a vaccine against any disease. Certainly we did for polio and smallpox. And yet here we are 15 years into the AIDS epidemic, and we don't have a vaccine against HIV. We don't have a vaccine against malaria or even an effective one against tuberculosis. Why is it so hard to come up with the vaccine-prevention solution for these microbes?

LEDERBERG The short answer is evolution. Bugs have been living in a world in which we have been developing immunity to them, and some of them have been smart enough to evolve their own countermeasures. There's no guarantee that our immune mechanism will always be capable of coping with any highly evolved microbial threat.

You mentioned malaria, tuberculosis, and HIV. These are all characteristically very chronic diseases. They go on for many, many years. Antibodies obviously develop in their affected host and do not greatly influence the outcome of the disease.

HIPPOCRATES So the immune system is fighting; it's just not winning?

LEDERBERG It does not have all that it takes. The bugs have evolved their own countermeasures.

HIPPOCRATES What was your view of evolution before you looked through a microscope and saw two bacteria exchanging genetic material?

LEDERBERG Whoa. Big question. First of all, I'm not sure that we've ever had good microscopic views of the making of bacteria. The evidence for genetic exchange is genetic and biochemical, and it is essentially indirect evidence. We still don't have good figures of exactly what happens when you have a mating pair. You can see the pairs mating, but it's very, very hard to tell exactly how the DNA is getting from one cell to another.

Until 1946 there was a fixed consensus that bacteria were purely clonal. In fact, the class name for bacteria is *Schizomycetes:* fission fungi. That bacteria divide by fission was a myth that had been promulgated since the latter part of the 17th century, when [Antonie van] Leeuwenhoek first saw bacteria under a microscope.

[But genetic recombination in bacteria] makes one see that bacteria are really not that different from other types of organisms, and that they indulge in the kind of tricks that other organisms have for the acceleration of evolution.

HIPPOCRATES What you showed was that two bacteria can actually come together and merge their cytoplasm, the inner part of the bacteria. And then some of the DNA can go from one bacterium to the other, mixing their genetic material?

LEDERBERG *Mixing* is the appropriate term. If you have mating between two identical individuals, it has no genetic consequences. If you have mating between individuals who already differ, it can generate an enormous amount of [variation] by the rescrambling of the new factors each of them bring to the table.

HIPPOCRATES How real is the threat that something will come along, such as the Ebola virus, that could produce widespread death even in the wealthy parts of the world?

LEDERBERG I'd go back to the 1918 flu epidemic as an example because it actually happened. And from the point of view of population density and the propensity of people for travel, things have gotten worse. So of course [another pandemic] is going to happen. How well prepared are we? I've mentioned that there are remediation steps going on. Maybe

Seven recipients of the 1958 Nobel Prize awards in Stockholm. Dr. Tatum and George Beadle (far left) share the award for medicine and physiology with Dr. Lederberg (far right).

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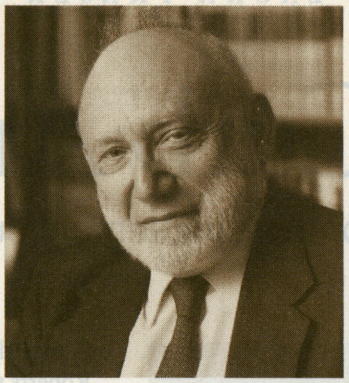
we'll be able to do a [slightly] better job this time in sustaining people who develop severe pneumonia with the supportive therapy they might need. But our hospitals will be absolutely swamped. Just on that basis, we won't be able to keep up.

It's a very real and very serious looming threat. It's one that's shared by everyone throughout the world. The key steps [to allow] improvement in vaccine are being contemplated, but they're not being adequately funded. They're lost in the noise about what we're going to be spending on health care. We're struggling to get tens of millions of dollars to deal with these public health issues. There is a great hoopla when there's a $40 million appropriation to the Centers for Disease Control and Prevention to improve its emerging infection program. That's $40 million out of a health budget in the hundreds of billions.



Dr. Lederberg today. President of the Rockefeller University for 12 years, he retired in 1990 but continues to do research there. He also enjoys time with his wife and two children.

HIPPOCRATES How has the science behind making vaccines evolved?

LEDERBERG Our basic technology of vaccine development has hardly changed in 40 years. It's actually empirical. You look for either attenuated strains—Louis Pasteur was doing that a hundred years ago—or you chemically [break down] the bacteria as with the split vaccine for proteases or viruses, which some of the flu vaccines are.

But that basic technology is 40 years old. We have learned a lot about cellular immunology since then. Almost none of that knowledge is used in today's vaccine development. And if we could improve our basic scientific foundation in vaccinology, we might even be able to go after the really tough nuts like malaria and tuberculosis.

HIPPOCRATES The public would like the government to do something about microbial outbreaks, but there's an odd dissonance between the government and the tenor of public and scientific concern. What's your read on this?

LEDERBERG One of the difficulties we face in trying to improve our public health is that we're asking for so little. There's no pork in it. Tens of millions is not really enough to excite attention when we're talking about billions in other spheres.

HIPPOCRATES There's a surprising sector of the policy world that has become excited and concerned about newly emerging diseases. That's the national security area: the Department of Defense, the Central Intelligence Agency, the White House. They seem to be saying, "We can't tell the difference between a naturally emerging new disease threat to the United States and one that's created by bioterrorists." How real is the threat?

LEDERBERG I am very much concerned about it, but I'm not sure that it changes the basic structure of the problem. Most of the nonmilitary responses that we require for dealing with a microbiological terrorist attack would be exactly the same as for a natural outbreak. So I don't see any great need to highlight the sensational aspects of bioterrorism. Now the bad guys, of course, made that lesson perfectly plain. After what happened on the Tokyo subway system in 1995 [when members of the Aum Shinrikyo cult several times released sarin, a fatal nerve gas], it's perfectly obvious that there are no bounds to what some people on the earth might be willing to do.

I'm glad the Defense Department is paying close attention to those issues. The discovery of huge stockpiles of anthrax and other biological weapons in Iraq has left it unmistakable that there are states still willing to put large resources into these weapons. There's a list of almost a dozen other countries that are involved, in one way or another, in biological warfare development. It is a matter that the national security system does have to be concerned about.

HIPPOCRATES You grew up in New York City and were a product of the public school system there.

LEDERBERG Very much so, at a time when it was a wonderful educational system. I went to Stuyvesant High School, which focused on math and science and was accessible by competitive examination. So unlike most of the schools in the city, there are students at Stuyvesant from all five boroughs, students who commute sometimes two hours if necessary to get to it. I lived up in Washington Heights, which was an hour's trip to Stuyvesant.

HIPPOCRATES You were committed to science at a young age.

LEDERBERG I've been committed to science ever since I can remember. I have no way to account for that. I came from a religious family, and my father was an Orthodox rabbi. There's a tradition of learning and of scholarship on both sides of my family that might be in some way responsible for how I was oriented. I've always taken science as almost a religious impulse to try to understand the world that I was living in. It's an important human drive, and it's one that has pushed me all of my life. H

SELECTED SOURCES 1. "Joshua Lederberg, Ph.D.: Nobel Laureate, Geneticist, and President Emeritus of the Rockefeller University," B. Lee Ligon, *Seminars in Pediatric Infectious Diseases,* vol. 9, no. 4, 1998. 2. "Joshua Lederberg: Advocate of a 'New Literacy,'" Bill Snyder, *Stanford MD,* Fall 1978. 3. "Genetic Recombination in *Escherichia coli,* 1946–1996: Disputation at Cold Spring Harbor," *Genetics,* October 1996.